# East meets West: ethnic differences in epidemiology and clinical behaviors of lung cancer between East Asians and Caucasians

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Review

# East meets West: ethnic differences in epidemiology and clinical behaviors of lung cancer between East Asians and Caucasians

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**Abstract**

Lung cancer is the leading cause of cancer death worldwide, with large variation of the incidence and mortality across regions. Although the mortality of lung cancer has been decreasing, or steady in the US, it has been increasing in Asia for the past two decades. Smoking is the leading cause of lung cancer, and other risk factors such as indoor coal burning, cooking fumes, and infections may play important roles in the development of lung cancer among Asian never smoking women. The median age of diagnosis in Asian patients with lung cancer is generally younger than Caucasian patients, particularly among never-smokers. Asians and Caucasians may have different genetic susceptibilities to lung cancer, as evidenced from candidate polymorphisms and genome-wide association studies. Recent epidemiologic studies and clinical trials have shown consistently that Asian ethnicity is a favorable prognostic factor for overall survival in non–small cell lung cancer (NSCLC), independent of smoking status. Compared with Caucasian patients with NSCLC, East Asian patients have a much higher prevalence of epidermal growth factor receptor (*EGFR*) mutation (approximately 30% vs. 7%, predominantly among patients with adenocarcinoma and never-smokers), a lower prevalence of *K-Ras* mutation (less than 10% vs. 18%, predominantly among patients with adenocarcinoma and smokers), and higher proportion of patients who are responsive to EGFR tyrosine kinase inhibitors. The ethnic differences in epidemiology and clinical behaviors should be taken into account when conducting global clinical trials that include different ethnic populations.

**Key words** Lung cancer, ethnicity, Asian, EGFR, K-Ras

Lung cancer is the most commonly diagnosed cancer and the leading cause of cancer death worldwide. Lung cancer accounted for 13% (1.6 million) of the total cancer cases and 18% (1.4 million) of the cancer deaths in 2008[1]. There is a large variation of the incidence and mortality rate of lung caner in the world. In males, the highest lung cancer incidence rates are in Central/Eastern and Southern Europe (age-standardized rate, ASR, of 57 and 49 per 100 000, respectively), North America (ASR of 48.5 per 100 000), and Eastern Asia (ASR of 45 per 100 000). In females, the highest lung cancer incidence rates are found in North America (ASR of 35.8 per 100 000), Northern Europe (ASR of 21.8 per 100 000), and Eastern Asia (ASR of 19.9 per 100 000)[1]. The different incidence between men and women explains that in the US, approximately 45% of patients with NSCLC are women. However, in Eastern Asia, only 25% to 30% of patients with lung cancer are women[2,3].

## Epidemiology, Environment, and Genetic Susceptibility of Lung Cancer Patients in Asia and the US

There are other differences in characteristics of lung cancer patients between Asia and the US. Compared with patients in the US, Asian patients have generally a younger age of onset. In addition, the median age of Asian never-smoker patients (defined as never smoked or smoked less than 100 cigarettes in the lifetime) is significantly younger than ever-smoker patients; whereas in the US, the median age of never-smoker patients is

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significantly older than ever-smoker patients[3].

Smoking, the leading cause of lung cancer, accounts for 80% of the worldwide lung cancer burden in males and at least 50% of the burden in females[1]. In the US, approximately 10% of patients with lung cancer are never-smokers. In Asia, more than 30% of patients with lung cancer are never-smokers, and half or more lung cancer in women occur in never-smokers [3,4], suggesting that other risk factors may play an important role in the development of lung cancer.

Although cigarette smoking has peaked and declined in the US and several other areas, it has dramatically increased in the past two decades, and has yet to peak, in China and other developing countries[5]. Approximately 67% of males and 4% of females over 15 years of age in China are smokers, and a total of over 320 million Chinese smokers represents about one-third of all smokers worldwide[4]. Correspondingly, in the US, for the past two decades, the incidence and mortality of lung cancer have been decreasing among males and have remained steady among females. In China, the mortality of lung cancer has doubled between the 1970s and 1990s. Despite the lower prevalence of smoking, Chinese females have a higher prevalence of lung cancer (21.3 cases per 100 000 females) than do females in certain European countries such as Germany (16.4 cases per 100 000 females) and Italy (11.4 cases per 100 000 females), with an adult smoking prevalence of about 20%[1].

Other known risk factors for lung cancer include second hand smoking, diet and food supplements, alcohol drinking, exercise and physical activity, air pollution, and occupational/environmental exposure [5,6]. Indoor air pollution, mainly due to coal burning, may account for 13% of lung cancer in men and 17% of lung cancer in women in China[7]. For Chinese never smoking women, indoor cooking fumes may also contribute to the development of lung cancer[6]. In addition, infections such as tuberculosis and human papillomavirus may contribute to the development of lung cancer among Asian women[6].

In addition to different environmental exposures, family history and genetic susceptibility play important roles in the development of lung cancer[6]. Allele or genotype frequencies of genes in tobacco and drug metabolism (e.g. *CYP1A1*, *CYP2E1*, *CYP3A4, CYP3A5*, *mEH, NAT2, GSTT1*), DNA repair (e.g. *XRCC1*, *ERCC2, ERCC1*), and inflammation (e.g. *MMPs*, *Cox2*) may vary between different ethnic populations. Genome-wide association studies of lung cancer reported in predominantly Caucasian populations have identified three regions on chromosomes 5p15.33, 6p21.33, and 15q25 that have achieved genome-wide significance with $P$ values of $10^{-7}$ or lower[8-11]. A recent study concluded that common genetic variants in the TERT-CLPTM1L locus on chromosome 5p15.33 (rs2736100) are associated with risk for lung adenocarcinoma in never smoking Asian women, with substantially higher effect sizes than those previously reported in European smokers. However, there was no convincing evidence for association at chromosome 6p21.33 or 15q25 for lung cancer overall or for the adenocarcinoma subtype[12]. It is not clear whether the differences are due to different smoking status, or ethnicity, or some other variable(s).

## Survival and Prognostic Differences Between Lung Cancer Patients in Asia and the US

Several large epidemiologic studies suggested that Asian ethnicity is a favorable prognostic factor for overall survival (OS) of patients with non–small cell lung cancer (NSCLC, which accounts for ~85% of all lung cancers) and is independent of smoking status[2,3,13]. A recent retrospective population-based analysis of 15185 Japanese and 13 332 US Caucasian NSCLC patients treated between 1991 and 2001 suggested that Japanese ethnicity [vs. Caucasian: hazard ratio (HR) = 0.937, 95% confidence interval (CI)= 0.898–0.978, $P$ = 0.003] and never-smoker status (vs. ever-smoker: HR = 0.947, 95% CI = 0.909–0.987, $P$ = 0.010) are independent favorable factors for OS in addition to younger age, female gender, early stage, and treatment received[3]. The results were confirmed by a retrospective population-based analysis of 4622 Korean and 8846 US Caucasian NSCLC patients, with an adjusted hazard ratio of 0.869 ($P$ < 0.0001) for Korean vs. Caucasian patients[2]. Another retrospective population-based study of 20 140 NSCLC patients from the cancer surveillance programs of three Southern California counties suggested that even within the US, Asian ethnicity is an independent and favorable prognostic factor for OS (vs. non-Asian: HR = 0.861, 95% CI = 0.808–0.918), among both smokers (vs. non-Asian: HR = 0.867, 95% CI = 0.807–0.931) and never-smokers (vs. non-Asian: HR = 0.841, 95% CI = 0.728–0.971), adjusting for covariates such as age, gender, smoking status, pathology, and treatment[13]. Similar results were observed after stratification by stage. It is not clear whether these Asian American NSCLC patients were born in their native countries, and whether this ethnic difference will hold after the first generation. In another study with 1124 Asian American NSCLC patients including 5 major Asian American subgroups (Filipino, Vietnamese, Japanese, Chinese, and Korean), there was no statistically significant difference in clinicopathologic features or survival outcome between individual Asian American subgroups when analyzed according to smoking status,

nor survival difference between never-smokers and ever-smokers (11 vs. 10 months; $P = 0.30$)[14]. Except for Japanese American, most of the other ethnicity subgroups were born in their native countries. Analyses on Japanese patients suggested that the proportion of Japanese never-smokers was higher among native Japanese (17.2%) than non-native Japanese (11.6%) NSCLC patients[14].

In addition to epidemiologic studies, a recent randomized clinical trial of first-line chemotherapy among advanced epidermal growth factor receptor (EGFR)-expressing NSCLC patients showed that Asian patients have about 10 months longer OS compared with Caucasian patients regardless of treatment received, which is partially explained by different demographics (e.g. younger age of onset, higher proportion of never-smokers) and more frequent use of EGFR tyrosine kinase inhibitors (TKIs) in Asian patients (61% in Asian vs. 17% in Caucasian) in subsequent lines of treatment[15]. Another study analyzed results from three phase III trials suggesting a 3- to 5-month OS improvement in Japanese NSCLC patients compared to US patients who received carboplatin/paclitaxel as first-line treatment (12 or 14 months vs. 9 months; $P = 0.0006$). It has been suggested that differences in allelic distribution for genes involved in paclitaxel distribution and deposition (*CYP3A4* and *CYP3A5*) or DNA repair (*ERCC1* and *ERCC2*) may contribute to the different outcome between Japanese and US patients[16].

## Somatic Mutations Among Asian and US Patients with Lung Cancer

Treatment of NSCLC, particularly adenocarcinoma, is in the era of personalized medicine, with the focus on the development of innovative treatment options, particularly new target-based therapies directed against key signaling pathways involved in lung cancer growth and malignant progression. Many biomarkers, including *EGFR* and *K-Ras* somatic mutations, *ERCC1/RRM1* mRNA expression, and *EML-ALK4* translocation, have been tested for patient screening in clinical trials and/or clinical treatment. Among these, *EGFR* and *K-Ras* mutations have clearly demonstrated different characteristics between NSCLC patients in Asian and Caucasian populations[17-20].

### *EGFR* mutation

EGFR, a cell membrane receptor with tyrosine kinase activity, is expressed in most patients with NSCLC and plays an important role in cellular proliferation, inhibition of apoptosis, angiogenesis, metastatic potential, and chemoresistance. *EGFR* mutation has been proven to be a predictive biomarker for EGFR-TKIs, both for gefitinib and erlotinib, among both Asian and Western NSCLC patients. The IRESSA Pan-Asia Study (IPASS) phase III trial compared first-line carboplatin and paclitaxel with gefitinib in East Asian never-smokers or former light smokers with lung adenocarcinoma [21]. The trial demonstrated the superiority of gefitinib compared with carboplatin and paclitaxel in overall response rate (RR, 43.0% vs. 32.2%; odds ratio = 1.59, 95% CI = 1.25–2.01, $P < 0.001$), progression-free survival (PFS, HR = 0.74, 95% CI= 0.65–0.85, $P < 0.001$), and quality of life, as well as a lower rate of toxicity in the intent-to-treat patient population. In the subgroup of patients with an *EGFR* mutation, the PFS was significantly longer in the gefitinib arm than in the carboplatin and paclitaxel arm (HR = 0.48, 95% CI = 0.36–0.64, $P < 0.001$). In contrast, in patients with wild-type *EGFR*, the PFS was significantly shorter in the gefitinib arm than in the carboplatin and paclitaxel arm (HR = 2.85, 95% CI = 2.05–3.98, $P < 0.001$). The final analysis of IPASS study showed that median OS was similar between gefitinib and carboplatin/paclitaxel arms in the overall population (18.8 vs. 17.4 months, HR = 0.90, 95% CI = 0.79–1.02, $P = 0.11$), in *EGFR* mutant patients (21.6 vs. 21.9 months, HR = 1.00, 95% CI = 0.76–1.33), in *EGFR* wild-type patients (11.2 vs. 12.7 months, HR = 1.18, 95% CI = 0.86–1.63), and in patients whose *EGFR* mutation status was unknown (18.9 vs. 17.2 months, HR = 0.82, 95% CI = 0.70–0.96). Patients with *EGFR* mutation had better outcomes (median OS, 22 months) than those with wild-type *EGFR* (median OS, 11–12 months), regardless of which treatment arm they were in[22].

In another phase III OPTIMAL study presented by Zhou *et al.*[23] at the 2010 European Society for Medical Oncology (ESMO) conference, which randomized 165 Asian patients with advanced NSCLC to first-line erlotinib or gemcitabine/carboplatin chemotherapy doublet, the primary endpoint of PFS was 13.1 months in the erlotinib arm compared to only 4.6 months (HR of 0.16, $P < 0.0001$) in the chemotherapy doublet arm. The benefit provided by treatment with erlotinib was consistent in all subgroups stratified by age, smoking status, and gender.

In addition to Asian studies, a recent press release in January 2011 announced that in the interim analysis of the phase III EURTAC trial by the Spanish Lung Cancer Group with researchers in France and Italy, erlotinib significantly extended PFS among newly diagnosed NSCLC patients with EGFR-activating mutations when compared with a platinum-based chemotherapy regimen. It is the first phase III study to show a PFS benefit with first-line treatment in a Western population with advanced NSCLC harboring *EGFR* mutations, with the full data to be presented or published soon. An Online Tumor Registry of five clinical trials from the US and

Europe, in which chemotherapy-naive patients with advanced NSCLC were treated with an EGFR-TKI (gefitinib or erlotinib), 56 (67%) *EGFR* mutant patients achieved an objective response, with a median PFS of 11.8 months and a median OS of 23.9 months. For the 83 patients with wild-type *EGFR* and wild-type *K-Ras*, the RR was 5%, the median PFS was 3.1 months, and the median OS was 11.8 months. Among the 41 patients with wild-type *EGFR* and mutated *K-Ras*, RR was 0%, PFS was 3.3 months, and median OS was 13 months. Patients with *EGFR* exon 19 deletions had a longer PFS (14.6 vs. 9.7 months, $P$ = 0.02) and OS (30.8 vs. 14.8 months, $P$ < 0.001) than those with the L858R mutation[24].

Several demographic and pathological factors are associated with *EGFR* mutation prevalence. *EGFR* mutation is mainly observed among patients with adenocarcionoma, never-smokers, and Eastern Asian ethnicity. Among Asian patients, the overall prevalence of *EGFR* mutations (i.e. exons 18–22) is approximately 30% overall, 47% among patients with adenocarcinoma, and 56% among never-smokers. Among Caucasians, the average *EGFR* mutation prevalence is approximately 7% overall, 13% among patients with adenocarcinoma, and 35% among never-smokers[20]. The reason for the high frequency of *EGFR* mutations in Asian patients is unclear, and it is suggested that the CA simple sequence repeat 1 (CA-SSR1), a highly polymorphic locus containing 14 to 21 CA dinucleotide repeats, and polymorphisms in the *EGFR* promoter regions may play an important role. Studies have suggested that many Asians have polymorphic types that lead to a decreased intrinsic production of EGFR protein. If a certain critical level of EGFR is required to drive the cell toward a malignant phenotype, another mechanism including activating mutations of *EGFR* and/or autonomously activating downstream signaling may be required for the development of lung cancer among Asians[19,20].

## *K-Ras* mutation

The Ras proteins belong to the small guanosine triphosphatase (GTPase) superfamily. Each *Ras* gene has a predilection to specific tumors, with *K-Ras* predominantly found in colorectal, lung, pancreatic, ovarian, endometrial, gastric, and brain cancers, *H-Ras* in bladder cancer, and *N-Ras* in melanoma and leukemia. More than 95% of *Ras* mutations are in codons 12/13 of exon 2. *Ras* mutation results in activation of Ras protein, inhibition of GTPase activity, resistance to upstream inhibitors, and resistance to EGFR inhibitors.

The overall *K-Ras* mutation prevalence in patients with NSCLC is approximately 16% (or 18% among Caucasian populations), based on two recent meta-analyses of 22 studies with 1470 NSCLC patients treated with EGFR-TKIs[17,18]. *K-Ras* mutation is predominantly observed among Caucasian patients with adenocarcinoma (~26% vs. 16% among patients with NSCLC of other cell types, and very uncommon among patients with squamous cell carcinoma) and ever-smokers (25% vs. 6% among never-smokers)[17,18]. A recent study on 482 patients with lung adenocarcinoma (mainly Caucasians) suggested a 15% of *K-Ras* mutation prevalence among never-smokers, 22% among former smokers, and 25% among current smokers ($P$ = 0.12)[25]. In addition, never-smokers were significantly more likely than former or current smokers to have a transition mutation (G to A) rather than the transversion mutations (G to T or G to C) known to be smoking-related ($P$ < 0.0001)[25]. Among Eastern Asian patients with NSCLC, *K-Ras* mutation prevalence is generally less than 10% and is very rare among squamous cell carcinoma and never-smoker patients[26]. Asbestos exposure may be associated with *K-Ras* mutation; however, data are limited.

There are inconclusive results on whether *K-Ras* mutation is a prognostic or predictive factor of advanced NSCLC treated with chemotherapy[27]. *K-Ras* mutant patients with NSCLC do not generally respond to EGFR-TKIs, and the predictive power of *K-Ras* mutations for EGFR-TKIs sensitivity was higher in Asians than in Caucasians[18]. However, due to a mutually exclusive relationship between *K-Ras* and *EGFR* mutation, and no survival difference between mutant and wild-type K-Ras among EGFR wild-type patients with NSCLC[24], the clinical usefulness of *K-Ras* mutation as a predictor of EGFR-TKIs sensitivity in patients with NSCLC is limited[18].

## *EML4-ALK* translocation

A recent breakthrough in NSCLC treatment is the discovery of the *EML4-ALK* fusion-type tyrosine kinase in patients with NSCLC (mostly adenocarcinoma) and the dramatic response of *ELM4-ALK*$^+$ patients to crizotinib in clinical trials[28,29]. Replacement of the extracellular and trans-membrane domain of ALK with a region of EML4 results in constitutive dimerization of the kinase domain and thereby a consequent increase in its catalytic activity[28]. In a phase I study with 82 advanced NSCLC patients who have mostly failed multiple lines of therapy, the overall response rate of *ELM4-ALK*$^+$ patients to crizotinib was 57% (46 confirmed partial responses and 1 confirmed complete response), and 27 patients (33%) had stable disease; 63 patients (77%) were continuing to receive crizotinib at the time of data cutoff, and the estimated 6-month progression-free survival rate was 72%, with no median for the study reached[29]. It is concluded that the inhibition of ALK in lung tumors with

the ALK rearrangement resulted in tumor shrinkage or stable disease in most patients.

The overall prevalence of *EML4-ALK* translocation among patients with NSCLC is 3% to 5%, and *EML4-ALK* translocation is mainly observed among patients who are typically never or light smokers, adenocarcinoma, younger age of onset, and wild-type *EGFR/K-Ras* (e.g. mutually exclusive with *EGFR* and *K-Ras* mutations)[28,30,31]. There is no strong evidence to suggest an ethnic difference of *EML4-ALK* translocation among patients with NSCLC. Because Eastern Asian patients with NSCLC have higher proportion of never-smokers and younger age of onset, it is likely that a higher prevalence of $ALK^+$ may be observed among Eastern Asian patients than Caucasian patients.

## Conclusions

Asian and Western patients with lung cancer have different characteristics for epidemiology (e.g. risk factors, demographics, and genetic susceptibility), clinical presentation, tumor biomarkers (e.g. *EGFR* and *K-Ras* mutation), response to target therapies, and prognosis. The exact mechanisms behind these differences are not clear. These ethnic differences should be taken into account when conducting global clinical trials that include different ethnic populations, where stratified analysis by race/ethnicity may need to be performed, and studies among Asian patients may need to be prioritized. In addition, Asia needs a guideline for the management of NSCLC because of differences in medical care, medical care insurance, ethnic variation, and drug approval lag within Asian countries compared with Western countries. It is suggested that Asian collaborative trials on treatment of NSCLC patients need to be started promptly to generate data from this important part of the world[32].

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